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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/939,230	08/24/2001	Alan David Wickenden	018512-006610US	5203

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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	**PAPER NUMBER**
1614	

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12/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/939,230	WICKENDEN ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of,this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-57,60-62,65-69 and 83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-57,60-62,65-69,83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10 October 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 45-57, 60-62, 65-69 and 83 are presented for examination.

A request for continued examination under 37 C.F.R. 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. 1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 C.F.R. 1.114. Applicant's payment and submission filed October 10, 2007 has been received and entered into the present application. Accordingly, prosecution has been reopened.

Applicant's Information Disclosure Statement (IDS) filed October 10, 2007 has been received and entered into the present application. As reflected by the attached, completed copy of form PTO/SB/08(A-B) (two pages total), the Examiner has considered the cited references.

Claims 45-57, 60-62, 65-69 and 83 are pending and under examination. Claim 63 is cancelled and claims 45, 62 and 65 are amended.

Applicant's arguments, filed October 10, 2007, have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement (New Grounds of Rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

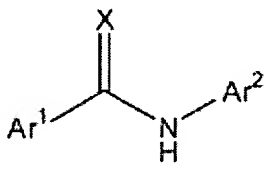
Claims 45-57, 60-62, 65-69 and 83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

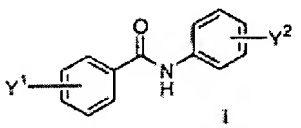
The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

The presently claimed invention is directed to a method for reducing anxiety (such as, e.g., where the anxiety is caused by panic disorder, generalized anxiety disorder, acute stress disorder or post-traumatic stress disorder; see present claim 46) in a subject in need thereof by increasing ion flow through KCNQ potassium channels in a cell comprising the step of administering to the subject a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound able to increase ion flow through KCNQ potassium channels, said composition administered to the subject in a potassium-channel opening amount, thereby reducing anxiety in the subject, wherein said compound has the following structural formula (defined in instant claim 1): 

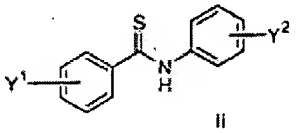
, wherein Ar2 is, specifically, a substituted or unsubstituted pyridyl group.

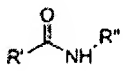
The instant claims require the administration of a compound of the formula *supra* in order to achieve the claimed therapeutic objective of reducing anxiety in a subject in need thereof via increasing ion flow through KCNQ potassium channels. However, the instant specification as originally filed lacks adequate guidance, direction or discussion to apprise the skilled artisan of the specific conditions and/or starting materials and/or reaction schema to be used to synthesize the claimed compounds of the above formula wherein Ar2 is, specifically, a substituted or unsubstituted pyridyl group. In the absence of such direction or guidance, the instant specification fails to provide adequate enabling disclosure to practice the full scope of the claimed subject matter.

Applicant states in the present specification at pages 27 that, "Compounds of the present invention can be prepared using readily available starting materials or known intermediates. Briefly, the synthesis of N-aryl benzamides herein or secondary amides herein involves formation of a single amide bond from a "carbonyl component" (typically a carboxylic acid, carboxylic acid chloride, ester or an activated form of a carboxylic acid, for example, a symmetrical or mixed anhydride) and an "amine component" (typically, an aniline, aniline derivative, amino heterocycle, and the like). General and specific procedures for the preparation of the present compounds are provided in the examples below." Exemplary synthetic reaction schemas are presented at page 28 for producing N-phenyl benzamides and the corresponding thioamides, each respectively of the following chemical structures:

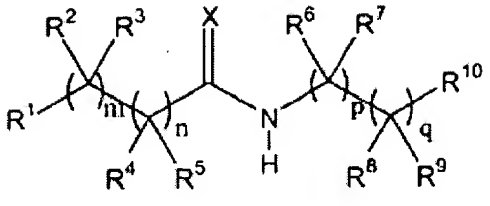


I and



II . In addition, Applicant presents a standard procedure for the production of secondary amide compounds of the formula 

at pages 29-30, wherein Applicant states that variable groups R' and R" represent the groups R1-(C(R2)(R3))m-(C(R4)(R5))n- and –(C(R6)(R7))p-(C(R8)(R9))q-R10, respectively, which appears to correspond to

Applicant's compounds of the formula  described at pages 7-8 of the instant specification.

However, while such disclosure has been fully and carefully considered, it is noted that this same disclosure lacks a clear teaching, direction or guidance as to how to prepare compounds wherein the aryl group bonded to the nitrogen atom of the amide linkage is a substituted or unsubstituted pyridyl group as now claimed (claim 45). Applicant disclosure presents synthetic methods for preparing a thioamide compound out of an N-phenyl benzamide compound, but conspicuously lacks a description of how one of ordinary skill in the art would go about actually synthesizing the N-phenyl benzamide compound and/or how such a process could have been simply modified so as to produce compounds of an N-pyridyl benzamide structure.

Furthermore, it is noted that the execution of chemical reactions is dependent upon numerous variable factors that are essential for producing the intended compound(s), such as, but not limited to, the starting materials to be employed, the temperature at which the reaction(s) should be carried out, solvents, reaction catalysts, molar quantities, surface area, pressure, activation energies, etc. In view of such a number of factors, and further in view of the high degree of variability for each single factor that must be taken into account in order to provide an accurate means for producing the claimed N-pyridyl benzamide compounds, the state of the art with regard to chemical reactions in general is highly complex and sufficiently unpredictable such that the skilled artisan would have been required to undertake undue experimentation to determine the exact conditions and manner and/or process of execution to arrive at those conditions that would have been amenable to actually producing the compounds of the formula presented in instant claim 45 as claimed in the absence of detailed guidance to this effect.

Absent such evidence or reasoning, and further absent any direction or guidance as to how the skilled artisan would go about synthesizing the claimed N-pyridyl benzamide compounds, one of ordinary skill in the art would have no alternative recourse but to undertake an exhaustive, and, thus, unduly burdensome, search for ways to synthesize this embodiment of the claimed invention suitable for use in practicing the claimed methods, particularly since the skilled artisan is faced with such a breadth and variety of possible starting materials and reaction schema from which to choose. In addition, it is not readily apparent that the prior art recognized methods of synthesizing the presently claimed compound at the time of the invention (or at least Applicant has failed to point to such information in a document that can be properly incorporated by reference) such that one of ordinary skill in the art would have been able to draw upon the knowledge already present in the prior art to execute the synthesis of the presently claimed compounds of claim 45, absent factual evidence to the contrary.

Though Applicant provides various examples directed to the expression of KCNQ2 and KCNQ3 mRNA in human dorsal root ganglion (Example 1); expression of recombinant KCNQ2/3 channel in chinese hamster ovary cells (Example 2); expression of endogenous KCNQ2/3 channel in dorsal root ganglions (Example 3); an *in vivo* formalin analgesia test (Example 4); an *in vivo* hotplate test for pain (Example 5); and an *in vivo* Geller conflict test for anxiolytics (Example 6), Applicant has failed to provide any working example (or at least provided any guidance within the disclosed working examples) directed to a possible method and/or manner of synthesis for the instantly claimed genus of compounds (or at least the benzanilide KCNQ channel opener used for the working examples). While the lack of a working embodiment cannot be the *sole* factor in determining enablement, the absence of substantial evidence commensurate in scope with the breadth of the presently claimed subject matter, in light of the unpredictable nature of the art and the limited direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole.

Moreover, the instant specification clearly fails to provide adequate direction and/or guidance as to how the claimed compounds may be used for treating the claimed disorder (i.e., reducing anxiety) with at least a reasonable expectation of successfully achieving the treatment of the same. The instant specification fails to present any evidence, either in the form of data or scientifically sound reasoning, which would provide such a reasonable expectation that the claimed compound would have been effective to treat the claimed disease state (i.e., anxiety). Though it is noted that Applicant need not necessarily demonstrate the precise manner in which the claimed therapeutic agent(s) ameliorate a particular disease state, such a mechanism must be elucidated in cases where Applicant relies upon a correlation between the particular activity of a compound (e.g., inhibition of a particular enzyme, binding to a particular receptor, etc.) and a reasonable expectation of efficacy in treating a particular disease.

In the instant case, Applicant relies upon the mechanism of action (i.e., increasing ion flow through KCNQ potassium channels in a cell) underlying the purported biological activity to establish that the genus of compounds instantly claimed would have been useful for reducing anxiety in a subject in need thereof. In other words, Applicant's inventive concept rests upon the correlation between the particular activity of the claimed compounds and a reasonable expectation of efficacy in treating the claimed disease. Though Applicant's Example 6, directed to an *in vivo* Geller conflict test for anxiolytics, demonstrates that the use of a compound with selective KCNQ2/3 channel opening activity increased punished responding in a dose-dependent manner by 40% or more at dosages of 30 and 56 mg/kg (an effect that is indicative of rapid-onset anxiolytic activity), Applicant has failed to demonstrate that the claimed compounds actually function to achieve the claimed activity of increasing ion flow through KCNQ potassium channels in a cell. The specification fails to present either via a working example(s) or a clear, scientifically sound explanation as to what, in fact, enables the ion flux increase through KCNQ potassium channels such that the skilled artisan would have been imbued with at least a reasonable expectation of predictability of action in treating the claimed disorder (i.e., reducing anxiety in a subject

in need thereof) by effecting this action using the full scope of compounds claimed. Absent such guidance, the experimentation required to determine if there is any activity of any of the compounds in treating the claimed disorder, and further, to determine, without needing to resort to random speculation, what therapeutic amounts would be available to even start testing for a therapeutic effect, would clearly be undue.

Although the instant specification states that the instantly claimed genus of compounds increase ion flow through KCNQ potassium channels, the disclosure fails to provide any mechanistic discussion or provide any evidence or data, preclinical or otherwise, supporting the concept that the instantly claimed compounds would, in fact, be effective to reduce anxiety by increasing ion flow through KCNQ potassium channels. In the absence of such discussion or evidence, it is clear that the instant specification fails to support the enablement of the instantly claimed compounds in functioning to increase ion flow through KCNQ potassium channels such that the skilled artisan would have reasonably expected that the compound(s), effective in this manner, would have functioned to treat the disorder presently claimed.

As stated in MPEP §2164.04[R-1], "Doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation." In the instant case, the information that is missing is a clear correlation between the claimed compound and its efficacy in treating the claimed disease, either through specific evidence in the form of data demonstrating such a fact or at least a sound mechanistic correlation between the claimed compound, *its ability to function in such a manner* and the amenability of the claimed disease state to treatment using an agent capable of functioning in this manner. Though one of skill in the art might very well known how to treat a patient with the claimed compound once a diagnosis had been made of the claimed disorder (i.e., anxiety), it remains that the instant specification conspicuously fails to provide any guidance or direction in support of the *reasonable expectation of success* in actually effecting the treatment of the claimed disease using the claimed compound in the

absence of any evidence supporting the allegation that the claimed compound is, in fact, effective to achieve such a therapeutic objective, either by reduction to practice or at least by elucidating the mechanism by which the claimed compound works and correlating such activity to therapeutic improvement of the claimed disease. In the absence of this information, the specification fails to provide adequate guidance and/or direction to one of skill in the art at the time of the invention that would have enabled such a person to practice the instantly claimed invention without having to resort to undue experimentation to determine how, in fact, one would achieve the instantly claimed therapeutic objective.

The basis for the present rejection is not simply that experimentation would be required, since it is clear from the state of the prior art and Applicant's disclosure and remarks that experimentation in this particular art is not at all uncommon, but that the experimentation required in order to practice the full scope of the invention would be *undue*. Please reference *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation is necessary, it is undue*." (emphasis added) Accordingly, in the absence of any adequate disclosure, direction or guidance as to how one would go about synthesizing the claimed compounds and/or using such compounds with a reasonable expectation of successfully treating the claimed disorder, it remains that the pharmaceutical, chemical and medical arts are notoriously complex such that methods of preparation and/or use would have been sufficiently unpredictable to warrant the need for undue experimentation to actually practice the full scope of the invention as instantly claimed.

In view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor or scientist with several years of experience in the art.

As the cited art and discussion of the above factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation or ability to make and use the full scope of the invention as instantly claimed, given the disclosure and

supporting examples provided in the present specification and that state of the art at the time of the invention. In order to actually achieve the claimed invention, it is clear from the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse but the impermissible burden of undue experimentation in order to practice the full scope of the embodiments presently claimed.

Conclusion

Rejection of claims 45-57, 60-62, 65-69 and 83 remains proper and is **maintained**.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leslie A. Royds
Patent Examiner
Art Unit 1614

December 12, 2007

12/15/07

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER